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## DECISION of 14 May 2001

Case Number:	T 1212/97
Boards of appeal:	3.3.4
Application Number:	84302368.0
IPC:	C12N015/13
Language of the proceedings:	EN
Published on CD-ROM LEGAL:	2001/002

Title of invention:

Recombinant immunoglobulin preparations, methods for their preparation, DNA sequences, expression vectors and recombinant host cells therefor

Applicant:

Genentech, Inc., et al

Opponent:

Bristol-Myers Company  
Roche Diagnostics GmbH  
Protein Design  
Ortho Pharmaceutical Corp.  
Celltech Limited

Headword:

Immunoglobulin preparations/GENENTECH

Articles & Rules:

EPC Art 123(2), EPC Art 054, EPC Art 056, EPC Art 083, EPC Art 084

Keyword:

Oral presentation - state of the art (no)  
Main request - claim 1 - sufficiency of disclosure (no)  
Main request - claim 16 - novelty (no)  
First auxiliary request - claim 1- sufficiency of disclosure (no)  
Second auxiliary request - novelty (yes)  
Inventive step (yes)  
Adaptation of the description

Decisions cited:

T 85/0292, T 87/0301, T 96/0890, T 97/0400

Catchword:

The information content made publicly available by a lecture cannot be put beyond reasonable doubt by any evidence of the lecturer alone, as the lecturer is in a quite different position to a member of the audience (see point 3 ff).

## Summary of Facts and Submissions

I. European patent No. 0 125 023 with the title "Recombinant immunoglobulin preparations, methods for their preparation, DNA sequences, expression vectors and recombinant host cells therefor" was granted with 23 claims based on European patent application No. 84 302 368.0, claiming priority from US 483457 of 8 April 1983.

Claims 1, 3, 9 and 22 read as follows:

"1. A method for preparing an immunoglobulin species having specificity for a particular identified antigen, the species comprising a chimeric immunoglobulin chain having constant and variable regions wherein a constant region is homologous to the corresponding constant region of an antibody of a first antibody class or first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second different antibody class or mammalian species; wherein

(a) a DNA sequence is prepared encoding said immunoglobulin species;

(b) the sequence is inserted into at least one replicable expression vector operably linked to a suitable promoter;

(c) at least one prokaryotic or eukaryotic host cell culture with which the promoter is compatible is transformed with at least one vector of (b); and

(d) the host cell is cultured and the immunoglobulin species is recovered from the host cell culture."

"3. A method according to claim 2 wherein the first mammalian species is human."

"9. The method of any preceding claim wherein the immunoglobulin species is a heavy chain, light chain or Fab immunoglobulin."

"22. A chimeric immunoglobulin species having specificity for a particular known antigen and having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species."

II. Six notices of opposition were filed. Opponents 2 withdrew their opposition when the case was pending before the Opposition Division. By a decision within the meaning of Article 102(1) EPC dated 16 October 1997, the Opposition Division revoked the patent.

III. The Appellants (Patentees) lodged an appeal against the decision of the opposition division, paid the appeal fee and filed a statement of grounds of appeal.

IV. Submissions were filed by the Appellants and the Respondents I, II, III and V (Opponents 1, 3, 4 and 6). A communication was sent by the Board drawing attention to the fact that four of the parties involved in these proceedings were also involved in the proceedings in case T 400/97, and suggesting that both proceedings be treated together. The parties consented to this. Respondents IV (Opponents 5) indicated that they would not be taking any further active part in the proceedings.

V. The Board sent a communication pursuant to Article 11(2) of the Rules of procedure of the Boards of Appeal conveying their preliminary non-binding opinion. Further exchanges of submissions followed.

VI. Oral proceedings in this case and in case T 400/97 took place from 22 to 26 May 2000. On the first day, the issue of what was the content of an oral disclosure by Dr Shulman (document M70 in the present case) was decided as it could be relevant to novelty and/or inventive step in both cases. The present case was dealt with on 24 to 26 May 2000.

VII. At oral proceedings, the Appellants filed a new main request together with two auxiliary requests. In the main request (claims 1 to 16), granted claims 2, 3, 18 to 21 and 23 were deleted and the other claims renumbered accordingly. Claims 1 and 16 (the latter being based on granted claim 22) read as follows:

"1. A method for preparing an immunoglobulin species having specificity for a particular identified antigen, the species comprising a chimeric immunoglobulin polypeptide chain having constant and variable regions wherein a constant region is homologous to the corresponding constant region of a human antibody and a variable region thereof is homologous to the variable region of an antibody derived from a second different mammalian species; wherein (hereafter) follow the same features (a) to (d) as in claim 1 as granted." (amendments compared to the granted claim emphasized by the Board)

"16. A chimeric immunoglobulin species having specificity for a particular known antigen comprising chimeric heavy and light polypeptide chains each having a constant region homologous to a corresponding constant region of a human antibody and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species." (amendments compared to the granted claim 22 emphasized by the Board)

Claim 7 differed from granted claim 9 in that the words "heavy chain, light chain or" were deleted.

In the first auxiliary request (claims 1 to 16), claims 1 and 16 read as follows:

.../...

"1. A method for preparing an immunoglobulin species having specificity for a particular identified antigen, the species comprising a chimeric immunoglobulin polypeptide chain having constant and variable regions wherein constant region is homologous to, and derived from, the corresponding constant region of a human antibody and variable region thereof is homologous to, and derived from, the variable region of a murine antibody, the said variable and constant regions of the chimeric immunoglobulin chain not being associated with one another in nature wherein (here follow the same features (a) to (d) as in claim 1 as granted)." (amendments compared to the granted claim 1 emphasized by the Board)

"16. A chimeric immunoglobulin species having specificity for a particular known antigen comprising chimeric heavy and light polypeptide chains each having a constant region homologous to, and derived from, a corresponding constant region of a human antibody and a variable region homologous to, and derived from, a variable region of a murine antibody, the said variable and constant regions not being associated with one another in nature." (amendments compared to the granted claim 22 emphasized by the Board)

All other claims were identical to the corresponding claims of the main request.

The only claim of the second auxiliary request submitted on 26 May 2000 read as follows:

"1. A non-glycosylated chimeric immunoglobulin species having specificity for a particular known antigen comprising chimeric heavy and light polypeptide chains each having a constant region from a human antibody and a variable region from a murine antibody."

VIII. At the end of these oral proceedings on 26 May 2000, the Chairwoman gave the decision that:

1. The decision under appeal is set aside.
2. The Appellant's main and first auxiliary claim requests are refused.
3. The claim of the second auxiliary claim request meets the requirements of the European Patent Convention.
4. The Appellant is given two months from today in which to file an amended description.

IX. An amended description was filed by the Appellants with letter dated 21 July 2000. With their submission dated 4 September 2000, 7 September 2000 and 13 November 2000, respectively, Respondents III, V and I disapproved of the amended description; Respondent V requested oral proceedings.

X. On 14 December 2000, the Board sent a communication to the parties together with an amended description which included the changes which, in the Board's provisional opinion, were necessary and appropriate to adapt the description to the remaining claim. The Appellants accepted the Board's suggestion for amendment with minor corrections whereas Respondents III and V objected to the version suggested by the Board. Oral proceedings with the sole issue of amending the description took place on 14 May 2001 where the Appellants and Respondents V were represented.

XI. The following documents are referred to in this decision:

- M1: Microbiology, Third Edition, Harper Intl. Eds., Chapter 17, Immunoglobulin Molecules and Genes, pages 337 to 380 1980,
- M7: Falkner, F.G. and Zachau, H.G., Nature, Vol. 298, pages 286 to 288, 15 July 1982,
- M9: Rice, D. and Baltimore, D., Proc. Natl. Acad. Sci. USA, Vol. 79, pages 7862 to 7865, December 1982,
- M10: Oi, V.T. et al., Proc. Natl. Acad. Sci. USA, Vol. 80, pages 825 to 829, February 1983,
- M11: Herzenberg, L.A. et al., Abstract of research plan sent to the Dep. of Health and Human Services, Public Health Service, February 1983,
- M12: EP-A-0 120 694,
- M13: Bobrzecka, K. et al., Immunology Letters, Vol. 2, pages 151 to 155, 1980,
- M15: Konieczny, L. et al., Haematologia, Vol. 14, No. 1, pages 95 to 99, 1981,
- M19: Skerra, A. and Plückthun, A., Science, Vol. 240, pages 1038 to 1041, 20 May 1988,
- M32: Ellison, J. et al., DNA, Vol. 1, No. 1, pages 11 to 18, 1981,
- M53: Ochi, A. et al., Nature, Vol. 302, pages 340 to 342, 24 March 1983,
- M59: Boss, M.A. et al., Nucleic Acids Research, Vol. 12 No. 9, pages 3791 to 3806, June 1984,
- M70: declaration of Dr Shulman and exhibits A to E thereto filed by Respondents I with submissions dated 30 August 1994,

.../...

P17: Cabilly, S. et al., Proc. Natl. Acad. Sci. USA, Vol.81, pages 3273 to 3277, 1984,

P23: Ochi, A. et al., Proc. Natl. Acad. Sci. USA, Vol. 80, pages 6351 to 6355, October 1983.

Dr Shulman's oral disclosure

XII. The Respondents I, II and III argued essentially that:

- It was beyond dispute that Dr Shulman gave the lecture as the Mallinckrodt Award lecture as part of the 198 Clinical Ligand Assay Society (CLAS) National Meeting on behalf of his colleague Dr Köhler who was unable to attend;
- The declarations made by Dr Shulman, and the evidence he gave before the Opposition Division in this case, clearly established what had been made available to the public by his lecture, including the slides shown. The evidence of Dr Shulman on the slides was corroborated by the evidence of the technician who prepared them; that on the content of the lecture was confirmed by Dr Hamilton, the organiser of the 1983 CLAS meeting, who was present at the lecture and could be considered as a member of the public;
- The evidence of Dr Shulman was wholly consistent with and thus confirmed by, the letter he wrote on Jan 1983 to Dr Hamilton, putting forward his intentions: "In my presentation I propose to discuss how one might combine hybridoma system with recombinant DNA and in vitro mutagenesis techniques to generate antibodies where the variable and constant regions are precisely specified... As we discussed last month, a title could be: "Monoclonal antibodies: the prospects for serious engineering". It is a lot of material to cover...". Furthermore, it was wholly consistent with and thus confirmed by the one sheet outline of his lecture given in evidence;
- Dr Shulman had particular reasons to remember the occasion of the lecture, because unlike his colleagues he did not wish to be involved in patenting;
- The evidence put forward on behalf of the Patentees, was insufficient to outweigh Dr Shulman's clear evidence: that Dr Lyle, the only declarant who attended the lecture relied on by the Patentees, remembered the lecture only as a overview containing nothing new, could be attributable to the lapse of time or his lack of familiarity with the subject-matter; the evidence in the form of a declaration by a paralegal as to a telephone conversation she had with Dr Hamilton, and exhibiting questionnaires answered by others who attended the Mallinckrodt Award lecture was unsatisfactory in form and should be ignored, in particular it was unsafe as it could not be taken to reflect what those attending the lecture would have said if they had been properly questioned;
- The correct approach was for the Board to decide if the five slides relied on had been shown, and if so what member of the public would have understood;
- As Dr Shulman was an expert lecturer, the Board should deduce what was made available to the public from consideration of what an expert lecturer would have told his audience; also at least the contents of the letter of January 19, 1983 from Dr Shulman to Dr Hamilton should be treated as being made publicly available, as a sort of abstract of the lecture.
- The situation of a lecture was analogous to that of a journal accepted as having been made publicly available as of a particular date on proof of a public library having date-stamped the copy it received: it was sufficient to prove that the lecture contained the information, irrespective of whether any member of the audience actually did write down the information or understand it. If the Board had any doubts on Dr Shulman's evidence, he was available to give evidence at the oral proceedings, and should be heard.

XIII. The Patentees essentially argued that:

- The CLAS was an unlikely forum to choose to make a disclosure on heterogeneous Ig molecules;
- There was no mention of chimeric antibody or scheme for expressing it in Dr Shulman's letter to Dr Hamilton;
- In accordance with the case law (eg. T 890/96 of 9 September 1996), for a lecture what was made public must be established beyond reasonable doubt;
- For so fundamental a disclosure, it was remarkable that no one picked it up if it was made. In addition, the surrounding circumstances rendered it extremely unlikely that it was indeed made, namely that Dr Shulman was working on a project with collaborators and never got their consent to publication at this lecture, nor even informed them that he was going to make any disclosure relating to the collaborative work;
- If a disclosure was made at all at the lecture, Dr Shulman did not acknowledge any contribution by his collaborators: this contrasted strangely with the fact that when the work of the collaboration was expressly made public in 1984 in Nature all were expressly named. Not one of Dr Shulman's collaborators confirmed that this talk was given;
- It could not be safely concluded that Dr Shulman showed slide 534L on the expression system. There was no reliable record of anyone in audience having seen the slide or understood the subject: in fact the weight of evidence was against this, namely the declaration by Dr Lyle that he had attended the lecture, had heard nothing new, and did not recall any mention of the matters set out in Dr Shulman's declaration and specifically relied on by the Opponents

...

and the declaration by the paralegal exhibiting questionnaires completed by others who attended the lecture, which others again did not recall the lecture as providing anything not previously known;

- it was never suggested that the audience were given copies of notes or slides. No details were provided how long any slide was shown for: it may have been shown for so short a time that nobody could take note of its content;
- the evidence of Dr Hamilton was unsafe and contradictory, both in itself and in view of the evidence given by the paralegal of telephone conversation with him, to the effect that Dr Hamilton would be unable to remember anything about the 1983 CLAS meeting other than what related to the three talks he himself gave at that meeting;

Submissions regarding the substantive issues

XIV. The submissions by the Appellants in writing and during oral proceedings insofar as they are relevant to the present decision are essentially the following:

Main request

Article 84 EPC

- The skilled person would have no problems in understanding the terms "polypeptide" (claims 1 and 16) and "chimeric light and heavy polypeptide chains" (claim 16) as the earlier was a basic term of molecular biology, and common general knowledge in relation to the latter was disclosed on pages 5 and 6 of the patent application as filed.

- The terms "human" qualifying the antibody source of the constant region in claim 1 and "chimeric" qualifying the immunoglobulin (Ig) species in claim 16 were already qualifying the same entities in granted claims 3 and 22. They were not open to objections for lack of clarity.

- Claim 1 left open the possibility that the Ig species to be prepared could comprise one or two chains. This did not imply that this molecule was not defined: indeed, it had to be chimeric and to have specificity for a defined antigen.

Article 83 EPC; sufficiency of disclosure in relation to the subject-matter of claim 1:

(a) The patent specification showed that non-chimeric Ig chains could be produced in *E. coli* and assembled into functional Igs. No evidence was provided by the Respondents that functional chimeric Ig molecules could not be produced in exactly the same manner. There were many post-published documents (documents (P17), (M59), (M19)) which attested that recombinant Igs could be obtained in *E. coli*.

(b) There was a substantial section in the patent specification on how to prepare Ig chains in mammalian cells. In particular, host cells, promoters and expression vectors were explicitly mentioned on pages 18 and 19. Furthermore the state of the art at the priority date ((M9), (M10), (M7)) provided adequate information for the skilled person to be able to choose a suitable expression system.

(c) The invention consisted in the novel and inventive concept of recombinant chimeric Igs. They were entitled to broad protection for their new and inventive concept. They had shown that recombinant Igs could be made in *E. coli*. They had thus provided a proof of principle that these molecules could be made by recombinant means in general. It was allowable to put forward a claim to a general method of producing these Igs as long as one way was provided which could be followed to produce them. The findings in respect of how to assess sufficiency of disclosure in the earlier case T 292/85 (OJ EPO 1989, 275), paragraph 3.1.5 applied to the present case.

Article 54 EPC; novelty of claim 16:

- It would be obvious to the skilled person that the purpose of the invention was to make antibodies (Abs) which were different from natural Abs so that the claim would be read as not including the latter.

- The argument by the Respondents that natural Abs fell within the scope of claim 16 because they were all homologous to each other in the constant and in the variable regions of their light and heavy chains did not take into account that the claimed Ig was also required to be chimeric. The term "chimeric" meant that the constant and the variable regions of each chain came from different species. This could readily be seen in their sequences, which comprise amino acids in some positions which were specific of the species these sequences originated from. A way was, thus available to differentiate chimeric Abs from natural ones.

Further evidence that natural antibodies were specific of the species they were synthesized in, was that the body reacted differently depending on the origin of the antibodies it was presented with.

First auxiliary request

Article 83 EPC

The arguments presented in favor of sufficiency of disclosure in relation to claim 1 of the main request were also valid for claim 1 of the first auxiliary request.

Second auxiliary request

.../...

#### Article 123(2) EPC

The objections made by the Respondents under Article 123(2) EPC (section XV below) failed because ~~it would be implicit to the skilled person~~ firstly, that chimeric as well as non-chimeric Abs could be made in non-glycosylated form according to Example 3 and, secondly, that not only murine hybridoma Abs but murine Abs in general could be used as sources for the variable region. The disclosure of a murine variable/human constant chimeric heavy chain could be found on page 51, lines 2 to 4 of the application as filed.

#### Article 84 EPC

The skilled person would have no doubt that the terms "from a human Ab" and "from a murine Ab" were meant to indicate the origin of the constant and the variable region. The term "chimeric" was already clear from the wording of the claim and, thus, it was not necessary to turn to the definition given in the patent specification to understand what the claim meant.

#### Article 83 EPC

The claim was to a product and not to a process. For enablement, it was enough that one way of making the product was provided. No serious doubts had been raised that everything covered by the claim could not be made.

#### Articles 54 and 56 EPC

No documents of the state of the art disclosed non-glycosylated, chimeric Igs. Furthermore, even if it was accepted that the concept of making chimeric Abs was in the public domain at the priority date, the skilled person had no reasonable expectation of success in obtaining non-glycosylated chimeric Abs as immunocompetent cells were believed to be the only cells to use to produce functional Igs (documents (M9), (M53) and (P23)).

#### Rule 67 EPC; reimbursement of appeal fee

- A substantial procedural violation had occurred in the course of oral proceedings before the Opposition Division because the Appellants had been denied an opportunity to file a claim request combining all possible allowable claims of the previously filed claim requests whereas they were led to believe that they would be given such an opportunity and the Opposition Division had not ruled that all claims of the previous claim requests were unallowable.

- The taking of evidence from the witness had also been unsatisfactory as the Opposition Division did not include a legal member and the questioning of the witness was conducted in a legally unsatisfactory manner. Since this evidence was taken as the closest prior art in the Opposition Division's finding of lack of inventive step, a substantial procedural violation had taken place.

For these reasons, the appeal fee should be refunded.

#### Adapting the description

- There was no need to delete from the patent specification the passages dealing with yeast or mammalian recombination systems (page 8, line 41 to page 9, line 29, page 11, lines 3 to 13) as the remaining claim was not a process claim but a product claim which would be infringed by someone producing the same product irrespective of the recombinant system used to produce it and notwithstanding the fact that the patent itself gave or not a sufficient disclosure of how to use said system.

- The claim was perfectly clear as to which chimeric Igs were meant to be protected. Accordingly, neither the passages in the patent specification relating to Fab fragments nor the passage bridging pages 6 and 7 giving a general definition of the expression "chimeric antibodies" introduced any unclarity as to the scope of the claim. These passages did not need to be deleted.

XV. The submissions by the Respondents in writing and during oral proceedings insofar as they are relevant to the present decision are essentially the following:

#### Main request

#### Article 84 EPC

- Claim 1: it was not obvious what further characterisation of the chimeric Ig chain resulted from the addition of the term "polypeptide" between the terms "chimeric immunoglobulin" and "chain". As for the term "human" added to qualify the antibody from which the constant region originated, it was intrinsically unclear because no information was available as to how many changes could be made to a human antibody before it ceased to be considered human. In addition, the skilled reader would be in doubt whether the Ig species to be prepared comprised one or two chains.

- Claim 16: the wording "comprising chimeric heavy and light polypeptide chains" introduced uncertainty as to whether the "chimericity" was within one chain or in the light and in the heavy chain, separately. Furthermore "chimeric" was defined in such a vague manner in the patent specification that it was not possible to determine which Ig molecules were comprised within the claim.

#### Article 83 EPC

In relation to the subject-matter of claim 1:

Claim 1 was extremely broad since it comprised preparing any chimeric Ig species in any host cells in any manner (secreted or otherwise). For these reasons, it was not acceptable that no complete example was given of the preparation of one Ig species.

(a) A chimeric light chain had not been obtained in E.coli.

The expression of the chimeric heavy chain could not be reproduced with the means at the skilled person's disposal at the filing date. The reconstitution of functional recombinant non-chimeric Igs had worked very poorly and the process could be expected to work even less satisfactorily with chimeric molecules.

(b) No instructions were provided to enable the skilled person to carry out the claimed method in mammalian cells. At the priority date, the available prior art (documents (M7), (M9), (M10)) showed that choosing the experimental conditions to produce by recombinant means a single, non-chimeric Ig chain in mammalian cells was not a routine matter.

(c) The production of chimeric Igs in eukaryotic cells (eg. in mammalian cells) and in E.coli cells by recovery from the cells themselves or from the cell culture medium was not enabled.

(d) The situation dealt with in the case T 292/85 (supra) was different from that encountered here as, there, one way of how to carry out the claimed invention was clearly indicated, contrary to the present case.

#### Article 54 EPC

- It was common general knowledge at the priority date that homology was a property shared by all natural Abs as they stemmed from a common ancestor molecule. This point was illustrated, in particular, in document (M32) (page 17 left-hand column) which disclosed that mouse and human Abs shared about 60% homology in the constant region of the heavy chain, whereas this homology increased to 81% in the constant region of the light chain (C). Accordingly natural Abs answered the definition of the Ig species in claim 16 as their constant regions were homologous to the "constant regions of a human antibody" and their variable regions were 100% homologous to the "variable regions of a Ab of a different mammalian species", it being the Ab from which they originated.

- Claim 16 also specified that the claimed Ig species was chimeric. The term "chimeric" was to be understood as defined in the application as filed in the passage bridging pages 11 and 12. This definition added no distinctive feature to the characterisation of the Ig species in terms of homology in the claim.

First auxiliary request

#### Article 83 EPC

The patent in suit provided no sufficient disclosure in relation to the process of claim 1 for the same reasons as presented in relation to the process of claim 1 of the main request.

Second auxiliary request

#### Article 123(2) EPC

There was no mention in the application as filed of chimeric antibodies in non-glycosylated form. In the same manner it was not disclosed that the variable region could come from any murine Ab but rather from an Ab obtained from murine hybridoma. The application as filed also failed to disclose a chimeric Ab where the human constant region was joined to the mouse variable region at the constant to variable junction. The requirements of Article 123(2) EPC were not fulfilled.

#### Article 84 EPC

The claim was unclear for the following reasons:

- the constant and variable regions were said to be "from a human" and "from a murine" Ab, respectively. The term "from" could be understood as meaning "derived from". Thus, it was unclear whether or not the claim comprised Igs with constant and variable regions homologous to the constant and variable regions of natural Abs.

- the wording "homologous to" implicitly remained in the claim because the term "chimeric" was still present which according to its definition in the patent specification, comprised this feature of "homology".

#### Article 83 EPC

The claim covered non-glycosylated Abs produced by secretion in bacteria as well as Ab fragments such as Fabs (which are naturally non-glycosylated) produced in eucaryotic cells. The patent in suit provided no guidance for the synthesis of such Abs. In addition, because of their extremely complicated structure, chimeric IgM would not be expected to be produced in bacteria.

.../...



## Article 54 EPC

The subject-matter of the claim was not novel over the disclosure of document (M12). This document disclosed the expression of non-chimeric Abs in E.coli at the same level as the patent in suit and it was clearly contemplated to produce chimeric mouse-human Abs. In addition, the claim was not novel over natural Abs since the presence of the term "chimeric" implied that the homology feature was retained and, thus, the reasoning in relation to claim 16 of the main request applied.

## Article 56 EPC

The breadth of the claim was such that there was no technical effect associated with most of its embodiments. Accordingly, there was no inventive step in relation to said embodiments. The only embodiments with which a technical effect was associated were those chimeric Abs, the structure of which comprised whole human constant regions and whole murine variable regions. The concept of such chimeric Abs was already known before the priority date from documents (M13), (M15) and (M11). In documents (M13) and (M15), chimeric, rabbit-human antibodies had been made by chemical methods. In the abstract of document (M11), it was stated that one of the purposes of the work presented was to produce interspecies, mouse-human variants. Once the concept was established, there were no difficulties in putting it into practice.

## Rule 67 EPC; refund of appeal fee

- The allegation by the Appellants that they were denied an opportunity to file a further claim request was not correct. At oral proceedings before the Opposition Division, the Chairman pointed out that, as far as the Opposition Division could see, the Appellants could not amend the claims to provide an allowable request but nonetheless gave them the opportunity to do so, which was declined.

- As for the allegation that the way evidence was taken amounted to a substantial procedural violation, it was also without foundation. The EPC did not specify that a legal member must be present to take the evidence; the Appellants were afforded an opportunity to ask questions. That these questions were deemed not to be relevant by the Opposition Division was a matter of judgment, not a matter of procedural violation.

## Adapting the description

- The claim as such was perfectly clear as it stood alone. Yet, the skilled person interested in the claimed subject-matter would also read the patent specification. The definition of "chimeric" given therein was broader than that in the claim, and non-chimeric Fab fragments were discussed on several occasions and even exemplified, but they were not comprised within the scope of the claim. The skilled person would thus be in doubt as to what products were within the scope of the claim. To avoid this uncertainty, the following passages should be deleted:

- page 6, lines 37 and 38: the sentence relating to "non-specific immunoglobulin".
- page 6, line 52 to page 7, line 5.
- page 8, line 8: "or modification thereof", line 19: "eukaryotic", line 24: "may also be" should be replaced by "are".
- all references to Fab protein (non-chimeric) and Example 5, Figure 13.
- The passage bridging page 8, line 41 to page 9, line 28 which the Board had deleted, should not be reintroduced as the use of yeast or mammalian cell lines was not enabled by the patent in suit.

XVI. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

- the main claim request or first auxiliary claim request, both submitted at oral proceedings on 24 May 2000, or
- the second auxiliary claim request submitted at oral proceedings on 26 May 2000, and
- the description submitted as main request or as auxiliary request both at oral proceedings on 14 May 2001.

They also requested reimbursement of the appeal fee.

The Respondents requested that the appeal be dismissed.

## Reasons for the Decision

### Dr Shulman's lecture

1. It is not in dispute that Dr Shulman gave a lecture, the Mallinckrodt Memorial lecture, at the 1983 CLAS meeting) some days before the priority date of the patent in suit to an audience of some one hundred to two hundred persons who would have received the information in the lecture as members of the public.

2. The question to resolve is whether there is any safe and satisfactory evidence as to the information content of what was made available to the public by the lecture, such that this information content can be taken into account

when assessing novelty and inventive step. For a prior publication to take away the novelty of a claim, according to the jurisprudence of the Boards of Appeal, the subject-matter of the claim must be clearly and unambiguously disclosed in the prior publication, and also in a manner which enabled the skilled person to carry it out. For prior publication to be relied on in assessing inventive step, it must be possible to determine the difference(s) between what was disclosed in the prior publication and what is claimed, and what hints the skilled person might have derived pointing to the claimed solution. The evidence relied on to establish the information content conveyed to the public by an ephemeral disclosure, such as a lecture, must be such that the Board is certain beyond any reasonable doubt that particular information was made available to the public. The Board cannot assess novelty and inventive step in relation to an alleged prior publication whose information content remains speculative.

3. For the evidence to be regarded as safe and satisfactory, it must unequivocally relate to what was made available to the public at the lecture. This is not a matter which this Board considers capable of being put beyond reasonable doubt by any evidence of the lecturer alone. The lecturer will have had the knowledge prior to the lecture, and will have prepared the lecture. His or her knowledge will not change as a result of the lecture, that of the audience may. The lecturer's evidence can be taken as defining the maximum amount of knowledge that may have been conveyed to the audience, but cannot be relied on to establish even what minimum of new knowledge was necessarily conveyed to the audience. The lecturer is in a quite different position to a member of the audience, and evidence of the lecturer's intentions or impression as to what was conveyed to the audience cannot even be treated as making out *prima facie* case that such information was actually made available to the public, certainly as regards to information which would have been new to the audience. Here the Board's approach differs completely from that of the Opposition Division who accepted the lecturer's evidence by itself as sufficient. This approach is also the reason why the Board declined to hear Dr Shulman at the oral proceedings before it, as further evidence from him would not serve to make up for the lack of evidence from the audience.

4. What evidence can be regarded as safely and satisfactorily establishing the information content made publicly available by a lecture will necessarily have to be judged on a case by case basis. Account must be taken of the fact that a lecture is ephemeral, so that the manner or speed of presentation may affect the comprehensibility of the lecture. Even an audio or video tape recording made of the lecture (unless themselves publicly available) would have to be treated with caution if several hearings or viewings are necessary to extract all information. Information appearing in each of the contemporary written notes made at the lecture by at least two members of the audience can usually be regarded as sufficient, whereas information in the notes of a single member of the audience might be inadequate as reflecting the thoughts of the listener rather than solely the content of the lecture. If the lecturer read his lecture from a typescript or manuscript, or the lecturer wrote up his lecture subsequently, and the lecturer was subsequently published in this form as part of the proceedings, then the written version might be taken as some evidence of the contents of the lecture, though with some caution as there would be no guarantee that a script was completely and comprehensibly read, or that a write-up was not amplified (compare decision T 890/96, *supra*). More useful would be a handout given to the public at the lecture, containing a summary of the most important parts of the lecture and copies of the slides shown. None of these types of evidence are available for Dr Shulman's lecture: he did not prepare a complete script, no hand-out of the contents was made, and Dr Shulman did not write up his lecture and there was no subsequent publication of specifically this lecture.

5. Apart from the evidence of Dr Shulman, the Respondents rely on a declaration by Dr Hamilton, who was the organiser of the 1983 CLAS meeting. Dr Hamilton did attend the lecture, but he had also as organiser corresponded and telephoned with Dr Shulman about the lecture prior to the CLAS meeting, and also at a dinner during the meeting. For this reason alone the Board finds itself unable to accept his evidence as necessarily referring to what he learnt as a member of the public attending the lecture. Secondly his declaration, made more than a decade after the lecture, states that he has read an earlier declaration of Dr Shulman in these proceedings. No explanation is given in his declaration as to whether anything in it relates to a recollection he had independently of reading Dr Shulman's declaration or why he feels able to recall matters with any certainty. The Board considers it relevant to be given information, why ten years after an event a witness considers he can reliably recollect what he learnt about a subject at a particular lecture, particularly where since that time he has acquired much greater familiarity with the subject. On the evidence provided the Board can only accept Dr Hamilton's evidence as confirming that nothing that Dr Shulman says is contrary to his recollections, but not as evidence of what an ordinary member of the audience at the lecture would have understood. The Board does not rely on the evidence given in form of a declaration by a paralegal concerning Dr Hamilton's memory, such hearsay evidence whilst maybe relatively easily obtainable, being inherently unsafe and unsatisfactory.

6. As there is no other evidence that supports the Respondent's case as to what was made publicly available at the lecture, the Board is already forced to the conclusion that there is no safe and satisfactory evidence that the information content of Dr Shulman's lecture as outlined in his declaration and exhibits thereto can be treated as having been made publicly available. Dr Shulman undoubtedly gave the lecture, but insofar as its information content went beyond what was already known in the art, or the comprehensible showing of any of the five slides specifically relied on is concerned, the Board is not satisfied on this on balance of probabilities, let alone beyond reasonable doubt.

7. In deference to the arguments of the various parties the following comments are made. For the Board it is the wrong approach to try and answer successive factual questions such as whether a slide was shown or not, and then what the audience would understand from it. The Board is concerned with the information content made available to the public. The burden of proof here is on the opponent. If there is no evidence on the information content from a member of the public present at the lecture, the Board is not concerned with the precise reason why this is so. Dr Shulman himself considered that he would be covering a lot of material, and there can be no presumption that he necessarily

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succeeded. There is no evidence here from a technician, based on his contemporary records and stating that he operated a slide projector at the lecture, confirming that each slide particularly relied on was shown for particular time. The only so called corroborative evidence of a technician relates to the slides being ordered in February 1983; but this is not evidence that they were actually shown.

8. The Board cannot reconstruct the information content based on any assumptions that Dr Shulman was an expert lecturer, and an expert lecturer who wished to explain the subject to an audience would have provided certain information, so Dr Shulman must have provided this information. This would be to assume the very thing which is to be proved. The circumstances of the lecture were unusual so the Board is not prepared to make any assumptions as to what happened. The lecture was not part of the ordinary 1983 CLAS meeting, but the Mallinckrodt Award Lecture. The Mallinckrodt Award had been given that year to Drs Köhler and Milstein to honour them for their work on hybridomas for producing monoclonal antibodies (work for which they later shared the 1984 Nobel prize for medicine), and Dr Shulman gave the lecture and received the award on behalf of his colleague Dr Köhler who was prevented. Whereas it can be presumed that the audience had some acquaintance with this hybridoma work, there is no evidence it contained anybody trying to apply genetic engineering techniques to hybridoma technology. The Board would agree with the Opponents' contention that at least some members of the large audience would be expected to be able to understand. But then the absence of any evidence helpful to the Opponents' case from a member of the audience is all the more surprising.

9. That Dr Shulman particularly remembered the occasion of the lecture, because unlike his colleagues he did not wish to be involved in patenting, can perhaps explain why he remembered the occasion, but is not evidence that he actually disclosed any work attributable to this collaboration in the lecture. There is no evidence that his collaborators reacted adversely to the lecture. In fact there is no evidence of anyone treating the lecture as a disclosure of something new. The printed publication of Dr Shulman and his collaborators appeared in Nature as an original publication. In the absence of conclusive evidence the Board is not prepared to find that it was in fact partly made available to the public already more than a year earlier at the lecture.

10. For the Board, the question involved here is essentially an appreciation of the evidence available in this particular case, and does involve any important question of law such as might require a reference to the Enlarged Board of Appeal. Certainly no conflict is seen with any existing Enlarged Board Decision. The Boards of Appeal of the European Patent Office do not apply a doctrine of binding precedent, so a discussion of the numerous cases cited by the parties would serve no useful purpose as the propositions which they establish are only of remote relevance to the present facts. The Board sees no useful analogy between evidence as to the information content of a lecture, and the situation where a journal is accepted as having been made publicly available as of a particular date on proof of a public library having date-stamped the copy it received. In the latter case there is no dispute as to information content, and the date stamp can be accepted provided there is evidence of the library's routine of date-stamping and making the journal available to the public. By contrast here the Board does not have a dispute as to the date of the lecture, but only as to its content. As stated above, on this the Board wants evidence from the audience, not from the lecturer. In the absence of evidence that any member of the audience actually did write down the information or understand it, the Board is not prepared to make any presumption as to the information content made publicly available.

11. Thus Dr Shulman's lecture insofar as the Opponents sought to rely on it is not considered by the Board to be state of the art in the proceedings.

12. Further, the Board cannot accede to the argument that the letter of January 19, 1983 of Dr Shulman to Dr Hamilton giving an outline of his proposed lecture, should itself be treated as being made available to the public. It was not written to Dr Hamilton as a member of the public but in his capacity as organiser of the conference. Where a letter has been written to further a joint interest of the sender and the recipient, it must prima facie be treated as private communication. Obviously here the letter was written preparatory to an intended publication of some information in the lecture. But a preparatory communication is not itself made available to the public at the time it is received, and here there is no evidence that anything in it that the Opponents might wish to rely on, was made available to the public at the lecture.

13. It was also argued that document (M11), an abstract of a research plan sent to the Canadian Department of Health and Human Services in February 1983 as part of an application for a research grant on behalf of a Dr Herzenberg and others should be treated as made publicly available as of February 1983. On the evidence put forward the Board can only conclude that while this document may have been open to public inspection at some date, there was no evidence that this was true prior to the filing date of the patent in suit. The purpose of such an application is to obtain a grant, not to make it available to the public, though this may be an incidental result. The public availability of such a document as from a particular date must be proved. Here the matter remains purely conjectural and document M11 cannot be treated as prior art.

Main request

Article 84 EPC; clarity:

14. The expressions "human antibody" (claim 1) and "chimeric Ig species" (claim 16) were already present in the corresponding granted claims 3 and 22. In accordance with the case law of the Boards of Appeal (T 301/87; OJ EPO 1990, 335), "when amendments are made to a patent during an opposition,.... Article 102(3) EPC does not allow objections to be made upon Article 84 EPC, if such objections do not arise out of the amendments made." Thus, the objections by the Respondents against the expressions mentioned above are not taken into consideration.

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15. In the Board's judgment, the objection raised for lack of clarity against the term "polypeptide" now qualifying the chimeric immunoglobulin ("polypeptide") chain in claim 1 or 16 is not convincing. Indeed, the term makes explicit what was already implicit from the common general knowledge i.e. that an immunoglobulin chain is a chain where amino-acids are linked together by peptide bonds i.e. is a polypeptide.

16. The further argument that the expression "chimeric light and heavy chains" (claim 16) leaves open the possibility that each chain would be composed of a portion of light chain and a portion of a heavy chain is not accepted. It is readily derivable from the application as filed (passage bridging pages 11 and 12) that chimeric molecules are not obtained in this manner but by recombining within the light chain, constant and variable regions of light chains of different origins and within the heavy chain, constant and variable regions of heavy chains of different origins.

17. Finally, the Board agrees with the Respondents that claim 1 comprises the preparation of Ig species made of one or of two chains but does not consider this point as raising clarity problems.

18. The claims of the main request are allowable under Article 84 EPC.

Article 54 EPC, novelty of claim 16:

19. The immunoglobulins of claim 16 are defined by three features: they are chimeric, they comprise a heavy and light chain, each of these chains has a constant region homologous to the constant region of a human Ab and variable region homologous to that of a second different mammalian species. The novelty of the claim was challenged on the basis of the common general knowledge at the priority date that Ig molecules comprised a heavy and a light chain, and that the light chains of Igs of different species had substantive homology in their constant as well as in their variable regions, a property which was shared by the heavy chains.

20. To decide whether or not this argument is valid, it is necessary to assess what the common knowledge was at the priority date. It must also be investigated whether the additional feature of the claimed Ig species of being "chimeric" may serve as a distinguishing feature over the prior art comprising all natural Abs.

21. The common knowledge is represented by document (M1), a review on "Immunoglobulin Molecules and Genes" published in 1980. It is also reflected in document (M32). Document (M1) discloses on page 377 that:

"1) Homology is greater between the C sequences of different species (e.g. man and mouse), and between the sequences of different species, than between the C and C of the same species.

2) Successive domains in the constant part of heavy chains of a particular class...have extensive homology ...with the corresponding domains of other species...

4) ...discernable low homology among all V sequences sets them apart from all the C sequences."

Document (M32) makes frequent references to the common general knowledge described in document (M1) (page 11 right hand column; passage bridging pages 14 and 15, page 17, 2nd paragraph). It shows, furthermore, that in the specific case of the human, constant heavy region (C 4), the level of homology to the mouse, constant heavy chain is 67%. Thus, it is concluded from the common general knowledge represented by documents (M1) and (M32) that natural Abs possess two of the features of the claimed Ig species mentioned in point 19 above.

22. The term "chimeric" is defined on page 11 of the patent specification: "'Chimeric antibodies' refers to those antibodies wherein one portion of each of the amino acid sequences of heavy and light chains is homologous to corresponding sequences in antibodies derived from a particular species ... while the remaining segment of the chains is homologous to corresponding sequences in another." This definition does not add any elements to the characterisation of the Ig species already spelt out in the claim and cannot serve to distinguish the claimed subject-matter from natural antibodies.

23. The Appellants argued that the term "chimeric" would be understood by the skilled person as implying that the various portions of the claimed Ig light and heavy chains came from different species, and that this was a distinguishing feature over natural Abs at the level of the amino-acid sequences of these chains. The Board agrees that natural Ig chains indeed contain species-associated amino acid residues as disclosed in document (M32), page 11 right-hand column. However, this does not imply that the claimed chimeric molecule can be distinguished from natural Ab by the fact that it would carry residues specific of natural Igs of two different species, for the following reasons:

- firstly, the claimed chimeric molecules are not obtained by combining constant and variable regions of natural Igs of different species but constant and variable regions of Igs homologous to constant and variable regions of natural Igs. This implies that the constant and/or variable regions of the claimed Igs need not have kept the allegedly distinguishing features of the natural ones.

- secondly, even if such distinguishing features existed, there is no evidence that, at the priority date, enough was known of the species specificity of some residues in the light and heavy chains to be able to identify on the basis of a molecular analysis the species, these chains originated from. It was argued instead that the body would recognize the origin of the Abs it was presented with, which the Board does not consider a suitable test for assessing novelty because there is no likelihood of obtaining consistent results.

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24. For these reasons, the Board decides that the subject-matter of claim 16 also encompasses natural antibodies and is, therefore, not novel in view of the common general knowledge at the priority date as disclosed in document (M1). This claim fails to fulfill the requirements of Article 54 EPC.

25. The main request is rejected for failing to fulfill the requirements of Article 54 EPC.

#### Considerations on sufficiency of disclosure

26. At oral proceedings, sufficiency of disclosure in relation to the subject-matter of claim 1 was also extensively discussed and interest was expressed that the Board's findings be given in writing. These findings are also relevant to sufficiency of disclosure in relation to the subject-matter of claim 1 of the first auxiliary request (point 32, below).

27. Claim 1 relates to a method for preparing chimeric Igs to be carried out in a prokaryotic or an eukaryotic cell culture whereby the Igs are recovered from the host cell culture. On pages 18 and 19 of the application as filed some general information is provided on mammalian expression systems: specific mammalian hosts are mentioned, the essential characteristics of the vectors and promoters are also described. In the Board's judgment, this information represents the general common knowledge on the cloning and expression of any genes in any mammalian cells.

28. No example is given of how to produce a chimeric Ig in a eukaryotic host cell culture. At the priority date, the recombinant expression of a non-chimeric light Ig chain had already been attempted. Documents (M7) and (M10) show that this expression can only be obtained by using specific combinations of host cells and promoters (SV40 promoter in some but not all non-lymphoid cells: document (M7); Ig promoter in some but not all lymphoid cells: document (M10)). Thus, even if it is accepted that chimeric light chains can be expressed in the same way as non-chimeric light chains, and that, in the light of the above mentioned documents, one such way of producing them is provided there remains that the claimed process is not enabled for the category of mammalian cells, in general. In addition, in order to reproduce the claimed invention, the skilled person would still be faced with the problems of expressing chimeric heavy chains in the same expression system as for the light chain and of recovering Ig fragments therefrom problems for the solution of which he/she would find no guidance, neither in the patent in suit itself, nor in the state of the art.

29. As far as expressing Igs in prokaryotic cells is concerned, the patent in suit discloses the production of non-chimeric Ig chains in E.coli in the form of inclusion bodies. Functional Igs are recovered by solubilizing and refolding the insoluble material. No mention is made of the possibility of producing a functional Ig, either directly from the cells or from the culture medium where it would have been secreted. It is only in 1988 that functional Igs were recovered from the culture medium of E.coli by using specific DNA constructs for the expression of the light and heavy chains (document (M19)). Thus, it is concluded that the co-expression and recovery of functional Igs directly from the bacterial cells or by secretion cannot be achieved in the absence of any technical information in the patent in suit.

30. The Appellants argued that the method used to produce the chimeric interspecies Igs was not important because the concept of making such Igs was new and inventive. In their view, a fair scope of protection having regard to the nature of the invention had to be of the same kind as that given in the allegedly analogous case T 292/85 (supra) where the Board decided that specific instructions need not be given as to how all possible component variants within the then used functional definition should be obtained (here being the glycosylated chimeric Igs produced in mammalian cells and the unglycosylated chimeric Igs produced in prokaryotes).

31. The Board, however, does not agree that the principle stated in decision T 292/85 (see supra) can apply here because no way is clearly indicated enabling the skilled person to perform the invention in the broad area claimed (see points 28 and 29 above). The competent Board in case T 292/85 accepted that not all ways of producing the claimed compounds needed to be disclosed (T 292/85, point 3.1.5 of the Reasons).

#### First auxiliary request

32. Claim 1 of this request differs from claim 1 of the main request in that the claimed method leads to the preparation of a chimeric Ig species where the constant and variable regions of each chain are derived from human and murine antibodies respectively. The considerations made by the Board under points 28 and 29 above as regards insufficiency of disclosure are equally valid in relation to the subject-matter of this claim as they do not depend on the origin of the chimeric Igs to be produced. The first auxiliary request is, thus, rejected under Article 100(b) EPC as not complying with the requirements of Article 83 EPC.

#### Second auxiliary request

##### Article 123(2)(3) EPC

33. The construction of recombinant DNAs encoding chimeric heavy and light chains is taught on page 28, paragraph D. and example E.4 of the application as filed. In examples E.1.9 and E.1.10, Abs are reconstituted from recombinant non-chimeric light and heavy chains expressed in E.coli (i.e. non glycosylated). In the Board's judgment, the skilled person would objectively derive from these teachings that Abs comprising recombinant chimeric light and heavy chains expressed in E.coli could be reconstituted in the same manner as described in the examples, which would lead to non-glycosylated, chimeric Igs. In addition, it is found that the teaching of using murine Abs as source of the variable region is derivable in a straightforward manner from the teaching on page 28 lines 30 and 31 of the

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application as filed to use murine hybridoma cells as a source for said region. Finally, support for a chimeric A where the human constant region is joined to the mouse variable region at the constant to variable junction is found on page 51, lines 2 to 5 of the application as filed. The requirements of Article 123(2) EPC are fulfilled.

34. The requirements of Article 123(3) EPC are also fulfilled as the corresponding granted claim has been restricted to a specific type of chimeric Ig: non-glycosylated, human-mouse Ig.

#### Article 84 EPC

35. The constant and variable regions of the claimed chimeric Ig are defined as being "from a human" and "from murine" Ab, respectively. In the Board's judgment, the skilled person would understand both these terms as meaning that the chimeric Ig comprises a natural human constant region joined to a natural murine variable region, and it is on this basis that the present decision is made. As the constant and variable regions are so defined, there is no need to turn to the definition of the word chimeric in the patent specification to interpret the claim which is clear. If this definition is nonetheless taken into account together with the claimed feature of the constant variable region being from a human and from a mouse Ab, respectively, the conclusion is reached that the level of homology envisaged in the claim is 100%. The requirements of Article 84 EPC are fulfilled.

#### Article 83 EPC

36. Examples E.1.7 and E.1.8 of the application as filed describe how to construct vectors for the expression of the light and heavy chains of a non-chimeric Ab, these vectors being used to transform E.coli in Example E.1.10. How to recover and to reconstitute the functional Ig molecule therefrom is disclosed in Example E3. This molecule is expected to be unglycosylated, as being produced in E.coli. The additional step of joining together DNAs encoding the heavy constant and variable regions of Igs of two different species to obtain a chimeric heavy chain is exemplified on pages 49 and 50 of the application as filed. In the Board's judgment, the average skilled person at the priority date would have been able to follow these teachings, which do not require more than routine techniques, to reproduce the claimed invention without undue burden. In particular, it would be within his/her ability to determine which restriction enzymes to use to produce the DNA encoding the chimeric Ab of his/her own choice. These restriction enzymes need not be those used in Example E.4. Thus, the argument that one of the restriction enzymes used in this example would not have been available in pure form at the priority date is not relevant to the issue of sufficiency of disclosure. No evidence was provided that associating light and heavy chains to form a functional chimeric Ig is in any way more difficult than associating non-chimeric chains.

37. The further objection that the patent in suit failed to provide a sufficient disclosure of how to produce non-glycosylated Igs by secretion, or of how to produce Fab Ig fragments in yeasts is also not relevant to the issue of sufficiency of disclosure as at least one way (Example E1.10) has been clearly indicated how to obtain the product which is claimed (T 292/85 see supra). In addition, no evidence was provided to back up the argument that some Ig molecules were of such complexity that they could not be expected to be expressed in E.coli.

38. Sufficiency of disclosure is, therefore, acknowledged.

#### Article 54 EPC; novelty

39. Novelty was challenged under Article 54(3)(4) EPC on the basis of document (M12), which is the patent on appeal under case number T 400/97 (see section IV above). In this parallel case, the Board decided on 24. May 2000 that the patent there in suit failed to disclose in an enabling manner the production in E.coli of functional Igs, i.e. of non-glycosylated Igs. The arguments and the parties involved being essentially the same in the two cases, the Board comes to the conclusion in this case that document (M12) not being enabling for the subject-matter here claimed cannot destroy novelty of the claim. Non-glycosylated chimeric Igs are also not disclosed in any of the other documents on file. Novelty is, thus, acknowledged.

#### Article 56 EPC

40. The closest prior art is document (M13) which is concerned with setting up a method of controlled re-arrangement of protein disulphides. The cross-bridging of Ig heavy chain fragments is exemplified. A combined molecule called "chimeric immunoglobulin" is obtained which is comprised of a heavy chain wherein the variable region and part of the constant region of a rabbit heavy chain is linked by means of an S-S bridge to the Fc part of the constant region of a human heavy chain. The molecule is said to have preserved antigen-binding activity. In document (M15), the authors of document (M13), when discussing the combined molecule, disclose that "Preliminary haemagglutination and complement fixation test suggest that some effector properties of human Fc may be preserved in chimeric Ig molecules".

41. Starting from the closest prior art, the objective problem to be solved can be defined as the provision of an alternative chimeric Ig having antigen-binding properties.

42. The solution provided is a non-glycosylated Ig molecule comprising both light and heavy chains wherein, in each chain, the variable region of a murine Ab and the constant region of a human Ab are linked by means of a peptide bond at the constant to variable junction.

43. In the Board's judgment, the technical teaching in document (M13) that fragments of Ig chains of different species may be assembled within one molecule is not damaging to inventive step considerations because the so called

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chimeric Ig has no structural similarities to the chimeric Ig within the meaning of the claim: its constant region is not species-specific, its primary structure is not that of a polypeptide, it does not exist as a dimer with a light chain, and it is glycosylated. And, besides, document (M13) only provides a means to achieve "chimericity" in the very specific circumstances where the molecules to be combined carry S-S bridges at the relevant location: for example such re-arrangement which led to the chimeric rabbit-human heavy chain could not be carried out on the light chain the constant region of which does not contain the relevant S-S bridges. It is, thus, concluded that the concept of chimeric immunoglobulin within the meaning given to this expression in the patent in suit is not disclosed in document (M13).

44. Were the opposite view to be held, as the Respondents did, that document (M13) discloses the concept of chimeric Igs because it teaches that fragments of Ig chains can be combined, it would still remain that chimeric Igs as intended in the patent in suit can only be made by rDNA techniques. In 1983, the natural mechanisms of synthesis of immunoglobulin had not been completely unravelled: document (M9), page 7862: "Although much is known about Ig gene structure, relatively little is known about the molecular mechanisms that control Ig gene expression.", document (M53), page 340: "The mechanisms responsible for the regulation of the expression of rearranged immunoglobulin genes are poorly understood." The attempts at expressing a single non-chimeric chain in a recombinant way had not always been successful (documents (M7) and (M10)), and the view was held that lymphoid cells would be the best host to produce functional Igs: document (M10), page 825: "Though a great deal has been learned about eukaryotic regulator sequences..., it would be preferable to transfer genes encoding proteins expressed during differentiation back into the cell type that normally expresses the gene of interest."; document (P23) (published six months after the priority date): "Because immunoglobulin production is a specialized function of cells of the B-lymphocyte lineage, it is expected that the conditions for proper gene expression will be provided only in appropriate immuno-competent cells." From these documents, it can be concluded that the skilled person did not have a reasonable expectation of success to produce functional chimeric Ig molecules in E.coli, i.e. to produce non-glycosylated chimeric Igs. The mentioning in document (M11) of the plan of obtaining interspecies (mouse-human) variants does not alter this conclusion.

45. Inventive step is acknowledged. The claim of the second auxiliary request fulfills the requirements for patentability.

#### Adapting the description

46. With the communication of 14 December 2000, the Board suggested some amendments to be carried out to put the description in conformity with the remaining claim of the second auxiliary request. At oral proceedings on 14 May 2001, Respondents V requested that, in addition to these amendments, the passages in the patent specification relating to the general definition of the terms "non-specific immunoglobulin" (page 6, lines 37 to 38), and "chimeric antibodies" (passage bridging page 6, line 52 to page 7, line 5) should also be deleted. Furthermore, in their opinion, the terms "or a modification thereof" and "eukaryotic" on page 8, lines 8 and 19, respectively, should be taken out as well as any reference to Fab fragments including Example E.5.2. The Appellants put forward as a main request that the passage of the granted patent bridging page 8, line 41 and page 9, line 28 which gives information on suitable yeast and mammalian expression systems, be reintroduced in the description amended as suggested by the Board in its communication of 14 December 2000 and, as an auxiliary request, that the description be amended in accordance with the Board's suggestion.

47. In the Board's judgment, none of the further amendments requested by Respondents V are necessary because, as they themselves admitted, the claim of the second auxiliary request is perfectly clear i.e. reading the description is not necessary to interpret any of the terms defining the claimed subject-matter and none of the remaining description makes unclear the scope of the claim. Although Fab molecules are not comprised within the claim, the example of how to produce a Fab fragment may be kept as a means to show which kind of rDNA techniques are generally relevant to performing the invention. As for reinserting the passage giving information on eucaryotic expression systems, it is not appropriate as the alternative held enabling by the Board was that of retrieving the claimed Ig species from E.coli.

48. The description filed by the Appellants at the end of oral proceedings on 14 May 2001 as an auxiliary request which takes into account the above findings and carries out corrections of some minor clerical errors is considered to be in conformity with the claim of the second auxiliary request.

#### Refund of the appeal fee

49. The Appellants argued that the Opposition Division committed a substantial procedural violation when, at oral proceedings, they refused to allow that a last request comprising claims which had not been found allowable be submitted, although they had assured the Appellants at the beginning of oral proceedings that such a request would be allowed. These submissions by the Appellants about what happened at oral proceedings are contradicted by the Respondents. The Board has no means to clarify this point. However, as the Appellants were allowed to put forward 1 auxiliary requests, the fact that the Opposition Division may have declined to accept an 18th auxiliary request appears to be a reasonable course of action reflecting its duty to be fair to all parties, which does not amount to a substantial procedural violation as required by Rule 67 EPC for the appeal fee to be re-imbursable.

50. As to whether or not the taking of evidence was done in a satisfactory manner, it was within the discretion of the Opposition Division to refuse questions as irrelevant, and the Board considers this discretion was exercised reasonably, so that no procedural violation took place. Also, there is no obligation under the EPC that a legally qualified examiner be present, so her absence cannot be treated as a procedural violation.

51. The request for refunding the appeal fee is refused.



## ORDER

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The Appellant's main and first auxiliary requests are refused.
3. The claim of the second auxiliary claim request meets the requirements of the European Patent Convention.
4. The matter is remitted to the first instance with the order to maintain the patent on the basis of the claim of the second auxiliary request submitted at oral proceedings on 26 May 2000, pages 1 to 23 of the description submitted as auxiliary request at oral proceedings on 14 May 2001, and the drawings as granted.
5. The request for re-imbursement of the appeal fee is refused.